DMAP-Catalyzed Benzannulation of Ethyl Propiolate with β-Dicarbonyl Moieties

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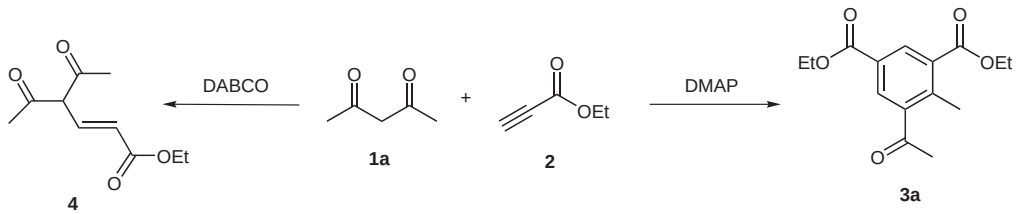
Abstract: 4-Dimethylaminopyridine (DMAP)-catalyzed benzannulation reaction of ethyl propiolate with β-dicarbonyl compounds at room temperature providing highly substituted benzenes is described.

Key words: ethyl propiolate, DMAP, benzannulation, β-dicarbonyl compounds

The regioselective generation of highly substituted benzenes represents a great challenge in synthetic chemistry.[1] Classical approaches use aromatic substitution, which introduces a substituent to a pre-existing arene.[2] However, these synthetic routes suffer from a long multi-step reaction sequence, low product yield, and poor regioselective control. Many modern methods for the synthesis of highly substituted aromatic compounds have been developed. These include transition-metal-catalyzed cycloaddition,[3,4] Dötz reaction,[5] carbonyl condensation reaction,[6] and electrocyclic reaction.[7] Nevertheless, the problems of regioselectivity and the need to prepare the starting materials always limit the general application of these methods to the synthesis of highly substituted benzenes.

1,3-Dicarbonyl compounds constitute an important class of synthetic intermediates, used as nucleophilic or electrophilic species in a variety of synthetic transformations.[8,9] Recently, we reported a Ph_3P-catalyzed α-C-addition of 1,3-dicarbonyl compounds to acetylenic ketones.[9b] However, no reaction occurred when ethyl propiolate (**2**) was used as the alkyne partner under similar conditions. When DMAP was tested as a catalyst in the reaction of 1,3-dicarbonyl compounds with ethyl propiolate, a new benzannulation reaction happened.[10,11] Treatment of 2,4-pentanedione with ethyl propiolate (**2**) in the presence of DMAP (20 mol%) gave the benzannulation product **3a** in 54% yield. This compound was satisfactorily characterized by NMR and MS spectroscopic analyses. This metal-free organocatalyzed process created a 1,2,3,5-tetrasubstituted benzene with three electron-withdrawing groups, which was difficult to construct by other conventional methods. This finding prompted us to explore the feasibility of the construction of polysubstituted benzenes based on utilization of readily available acetylenic esters and 1,3-dicarbonyl moieties.

We first chose ethyl propiolate and 2,4-pentanedione as the substrates to search for a potential catalyst and optimized reaction conditions (Table 1). It was observed that moderate yield was obtained when the reaction was stirred at room temperature for three days. Prolonging the reaction time resulted in no obvious effect on the reaction yield. However, the choice of solvent had some effects on the reaction. With THF, Et_2O, DMF, and DMSO as the solvent, the corresponding product **3a** was generated in a relatively lower yield. When toluene was used as the solvent, only a trace amount of **3a** was formed. Dichloromethane was found to be the best solvent for this reaction. In addition, the nature of amines played an important role in this reaction. The reaction of ethyl propiolate and 2,4-pentanedione catalyzed by Et_3N (20 mol%) could afford the desired product **3a** in 29% yield. Pyridine as a catalyst gave a complex mixture of unidentified products. When 1,4-diazabicyclo[2,2,2]octane (DABCO) was used in this reaction, a Michael adduct **4** between 2,4-pentanedione and ethyl propiolate was formed in 57% yield (Scheme 1). However, when the reaction was carried out using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a catalyst, no reaction was observed. Therefore, it seemed that the best reaction conditions were to carry out this reaction in dichloromethane with DMAP as a catalyst.



Scheme 1

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Table 1 Reaction of 2,4-Pentanedione (0.3 mmol) with Ethyl Propiolate (0.66 mmol) Catalyzed by Nitrogen Lewis Bases

Entry	Lewis base	Solvent	Time (d)	Yield (%)[a]
1	DMAP	CH_2Cl_2	1	24
2	DMAP	CH_2Cl_2	3	54
3	DMAP	CH_2Cl_2	5	58
4	DMAP	THF	3	36
5	DMAP	Et_2O	3	24
6	DMAP	DMF	3	22
7	DMAP	DMSO	3	21
8	DMAP	Toluene	3	trace
9	Et_3N	CH_2Cl_2	3	29
10	DABCO	CH_2Cl_2	1	57[b]
11	DBU	CH_2Cl_2	3	0

[a] Isolated yield.
[b] Yield of compound **4**.

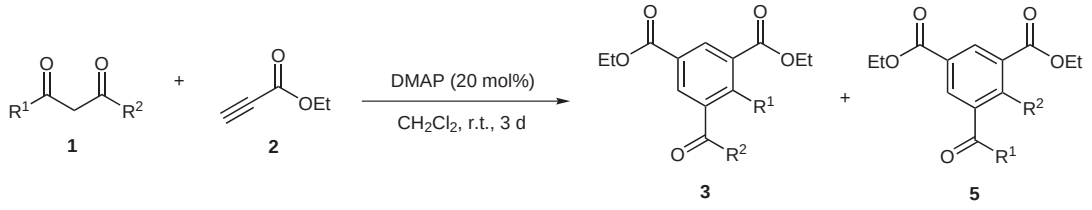
A variety of 1,3-dicarbonyl compounds were found to be applicable to this reaction to give product **3** in moderate to good yields under the optimized reaction conditions (Table 2 and Scheme 2).[12] Aromatic 1,3-diketones provided the corresponding products in good isolated yields. For example, exposure of 1-phenylbutane-1,3-dione (0.3 mmol) to ethyl propiolate (0.66 mmol) and DMAP (20 mol%) gave the desired product **3b** in 65% yield (Table 1, entry 2). Its regioisomer **5** could not be detected from the reaction mixture. The structure of compound **3b** was easily assigned on the basis of ^{13}C NMR spectral data as the ^{13}C carbon signal of the methyl group (R^2) was at $\delta = 30.4$. If the methyl group (R^2) was directly attached to the benzene ring, its carbon signal would have been positioned at about $\delta = 18.2$. The nature of the R^1 substituent on the benzene ring also had a remarkable effect on the reaction. As can be seen from Table 2, substrates bearing an electron-withdrawing group on the aromatic ring reacted smoothly and gave the desired product in good yield. On the other hand, substrates containing an electron-donating group reacted poorly. For example, when a methyl group was attached to the aromatic ring, the desired product **3g** was obtained in only 22% yield along with a small amount of the corresponding regioisomer **5** (<5%), whereas

Table 2 Reaction of β-Dicarbonyl Moieties with Ethyl Propiolate Catalyzed by DMAP

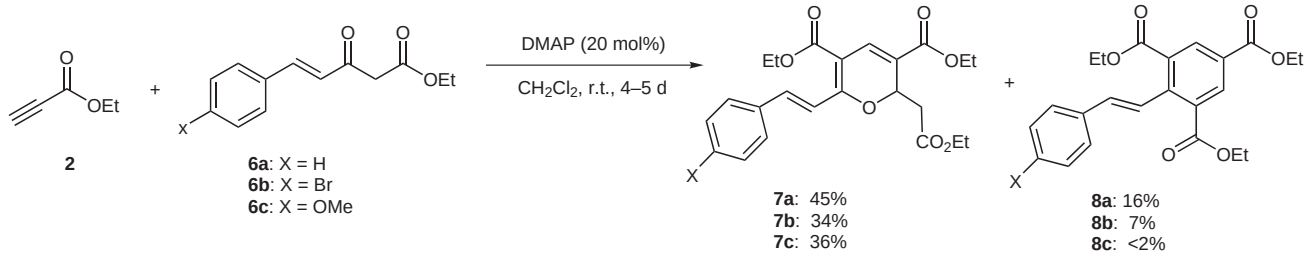
Entry	R^1	R^2	Product	Yield (%)[a]
1	Me	Me	**3a**	54
2	Ph	Me	**3b**	65
3	4-FC_6H_4	Me	**3c**	59
4	4-ClC_6H_4	Me	**3d**	69
5	4-BrC_6H_4	Me	**3e**	79
6	4-CNC_6H_4	Me	**3f**	68
7	4-MeC_6H_4	Me	**3g**	22[b]
8	4-$MeOC_6H_4$	Me	–	–[b]
9	2-$MeOC_6H_4$	Me	**3h**	62[b]
10	3-BrC_6H_4	Me	**3i**	51
11	3-$NO_2C_6H_4$	Me	**3j**	73
12	2-Naphthyl	Me	**3k**	43
13	Ph	Pr	**3l**	28
14	Ph	Ph	**3m**	62
15	4-ClC_6H_4	4-ClC_6H_4	**3n**	60
16	Ph	OEt	**3o**	45
17	4-MeC_6H_4	OEt	**3p**	51[b]
18	4-FC_6H_4	OEt	**3q**	63
19	4-BrC_6H_4	OEt	**3r**	62
20	4-CNC_6H_4	OEt	**3s**	64
21	2-Naphthyl	OEt	**3t**	54

[a] Isolated yield.
[b] Reaction for five days.

having a methoxy group at the *para* position completely retarded the reaction (Table 2, entry 8). Highly hindered 1,3-diketones were also identified as reluctant coupling partners in this reaction. When R^1 was phenyl, and R^2 was changed from a methyl to a propyl group, the yield of the corresponding product **3j** decreased to 28%, and a small amount of its isomer **5** was formed as well. When R^2 was the very bulky *tert*-butyl group, no reaction occurred under the same conditions.

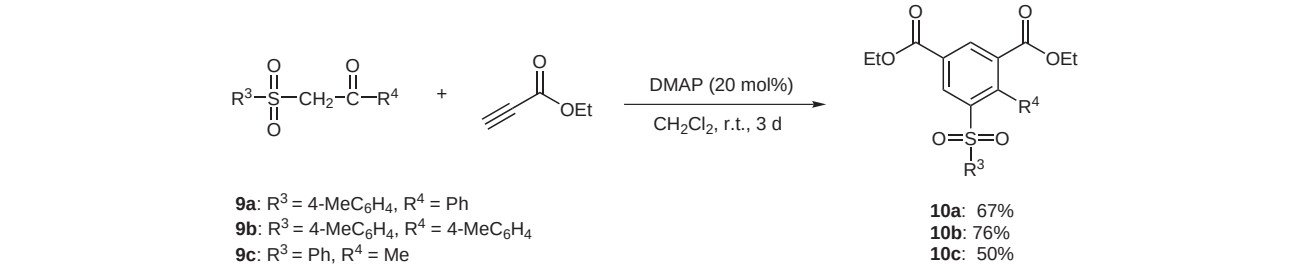


Scheme 2

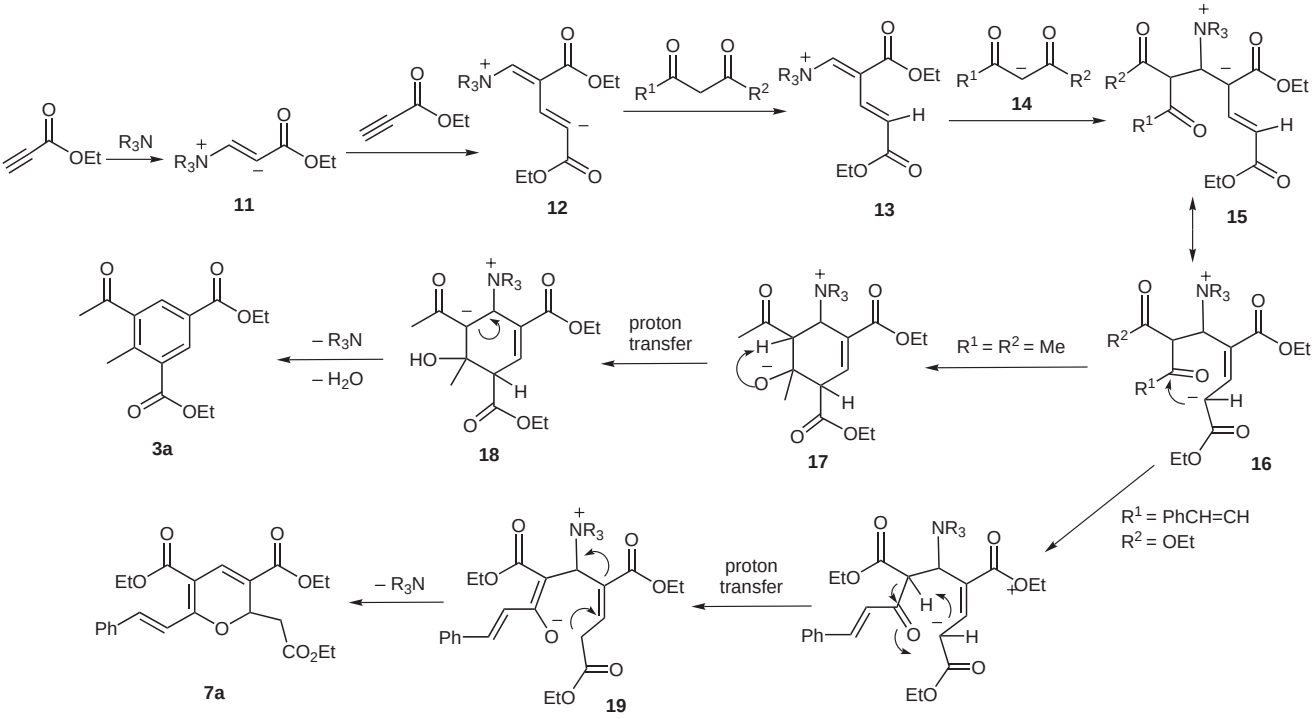


Scheme 3

Benzannulation of β-ketoesters with ethyl propiolate also proceeded smoothly to generate the corresponding products (Table 2, entries 16–21). Similar to 1,3-diketones, aromatic β-ketoesters with an electron-withdrawing group on the benzene ring gave the desired products in good yields. When ethyl acetoacetate was subjected to the same conditions, no reaction was observed even after prolonged reaction time (6 d). It was notable that a new compound **7a** was obtained as a major product along with a minor benzannulation product **8a** when β-ketoester **6a** derived from *trans*-cinnamaldehyde was used in this reaction. The substrate with a bromo or methoxyl group at the *para* position gave similar results (Scheme 3). On the basis of these findings, a new procedure for the synthesis of 1,2,3,5-tetrasubstituted benzenes has been developed. Since the starting materials are readily available, and the reaction conditions are mild, this methodology represents a powerful diversity route for the convergent construction of highly substituted benzenes. To the best of our knowledge, there is no report of organocatalyzed benzannulation of acetylenic esters with 1,3-dicarbonyl compounds.



Scheme 4 Reaction of β-ketosulfones and ethyl propiolate



Scheme 5 Possible reaction mechanisms

To further extend this reaction, β-ketosulfones were also applied to this reaction, and were found to undergo this benzannulation reaction. Hence, reaction of ethyl propiolate with β-ketosulfones **9a** and **9b** gave the corresponding products **10a** and **10b**, respectively, in 67% and 76% yields. Moderate yield was also obtained when alkyl β-ketosulfone **9c** was submitted to this reaction (Scheme 4).

A possible mechanism for the present catalytic reaction was proposed (Scheme 5). DMAP acted as a nucleophilic promoter to initiate the reaction and produced a zwitterionic intermediate **11**, which then added to a second ethyl propiolate to give the intermediate **12**. The intermediate **12** may then deprotonate the active methylene proton of the 1,3-dicarbonyl compound to generate the stabilized enolate **14** together with compound **13**. Enolate **14** was then added to **13**, followed by electron transfer to give the intermediate **16** and subsequent generation of **18** through intramolecular nucleophilic attack and proton transfer. DMAP and H_2O were eliminated from the intermediate **18** to afford the product **3a**. The intermediate **16** might undergo proton transfer to give enolate **19**, followed by Michael addition and elimination of Lewis base to generate product **7a**.

In summary, we have shown that 1,3-dicarbonyl compounds undergo a new benzannulation reaction with ethyl propiolate catalyzed by DMAP under mild conditions. This methodology offers a facile way to synthesize highly substituted benzenes from simple and commercially available starting materials.

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(12) **Typical Procedure**: A round-bottomed flask, equipped with a stirring bar, was charged with β-dicarbonyl moieties (0.3 mmol) and DMAP (0.06 mmol) in CH_2Cl_2 (3 mL) followed by ethyl propiolate (0.66 mmol) via a syringe. After stirring for the specific time at r.t., the reaction was concentrated under reduced pressure on a rotary evaporator and purified by silica gel chromatography using PE–EtOAc (10:1–5:1) to afford the corresponding product. Compound **3a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.39 (d, *J* = 1.7 Hz, 1 H), 8.18 (d, *J* = 1.7 Hz, 1 H), 4.30–4.39 (m, 4 H), 2.57 (s, 3 H), 2.55 (s, 3 H), 1.37 (t, *J* = 7.8 Hz, 6 H). ^{13}C NMR (75 Hz, $CDCl_3$): δ = 202.3, 167.2, 165.2, 142.1, 141.8, 133.7, 132.7, 130.9, 128.2, 61.71, 61.68, 30.7, 18.2, 14.4, 14.3. IR (neat): 1725, 1259 cm^{-1}. HRMS (ESI): *m*/*z* [M$^+$] calcd for $C_{15}H_{18}O_5$: 278.1154; found: 278.1147.
Compound **7a**: ^{1}H NMR (300 MHz, $CDCl_3$): d = 8.01 (d, *J* = 15.8 Hz, 1 H), 7.69 (s, 1 H), 7.55 (d, *J* = 7.9 Hz, 2 H), 7.34–7.43 (m, 4 H), 5.84 (dd, *J* = 3.2, 10.2 Hz, 1 H), 4.23–4.35 (m, 4 H), 4.15–4.19 (m, 2 H), 2.86 (dd, *J* = 10.2, 15.2 Hz, 1 H), 2.54 (dd, *J* = 3.2, 15.2 Hz, 1 H), 1.31–1.41 (m, 6 H), 1.24 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): d = 169.6, 165.0, 164.3, 162.1, 140.0, 136.0, 132.6, 129.9, 129.0, 128.2, 120.0, 117.9, 105.6, 71.9, 60.96, 60.92, 60.88, 37.8, 14.53, 14.45, 14.39. HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{23}H_{26}O_7$: 414.1679; found: 414.1674.
Compound **10a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.20 (d, *J* = 1.8 Hz, 1 H), 8.55 (d, *J* = 1.8 Hz, 1 H), 7.30 (m, 1 H), 7.12–7.17 (m, 2 H), 6.97–7.06 (m, 4 H), 6.87 (d, *J* = 7.5 Hz, 2 H), 4.49 (q, *J* = 7.2 Hz, 2 H), 3.99 (q, *J* = 7.2 Hz, 2 H), 2.33 (s, 3 H), 1.48 (t, *J* = 7.2 Hz, 3 H), 0.87 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (75 Hz, $CDCl_3$): δ = 166.7, 164.4, 144.8, 143.9, 142.1, 137.3, 136.6, 134.6, 134.2, 131.8, 130.5, 130.1, 129.2, 128.2, 127.9, 127.1, 62.1, 61.7, 21.6, 14.4, 13.6. IR (neat): 1727, 1248 cm^{-1}. HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{25}H_{24}O_6S$: 452.1294; found: 452.1302.

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